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10/758,554	01/14/2004	Christine Lindsay Mummery	17360	5975

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EXAMINER	
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1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,554	MUMMERY, CHRISTINE LINDSAY	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,46,50-54,60,61,63-65,68-71,87-89 and 133* is/are pending in the application.

4a) Of the above claim(s) *63 and 91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,46,50-54,60,61,64,65,68-71,87-89 and 133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 07/16/2010 have been fully considered. Claims 45-46, 50-54, 60-61, 63-65, 68-71, 87-89 and 133 are pending. The amendment has been entered. Claims 63, 91 are withdrawn. Claims 1-44, 47-49, 55-59, 62, 66-67, 72-86, 90, 92-132 are canceled.

Claims 45-46, 50-54, 60-61, 64-65, 68-71, 87-89 and 133 are under consideration.

The affidavit dated 07/16/2010 exhibits A and B has been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 51 stand rejected and claim 133 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection set forth in the previous office action dated is maintained for claim 51 and further applied to new claim 133 for the reasons of record and the remarks set forth below.

Claim 133 depends from claim 51.

New claim 133 is directed to the method of claim 51, wherein said embryonic cell is derived from visceral endoderm-like tissue and expresses alpha-feto protein.

Newly added claim 133 does not solve the issue the indefiniteness of the claim 51 because the claim includes elements not actually disclosed (those encompassed by "-like"), thereby rendering the scope of the claim unascertainable

Applicants argue that those skilled in the art would understand this phrase to mean that the tissues or cells in question have most of the characteristics of visceral endoderm tissue or cells, but are not visceral endoderm tissues or cells per se. The characteristics of visceral endoderm are clearly disclosed in the specification, e.g., on page 10, line 29-30; page 11, lines 1-10. Further, as evidenced by Mummery et al. (Differentiation 46: 51-60, 1991), visceral endoderm-like cells are understood to mean cells that express marker proteins characteristic of the differentiation of this early lineage, including alpha-feto protein which is expressed in all END2 cells and about 50% of EPI-7 and PSA-5E cells (also VE-like cells). Additional markers such as FT-1 are described in a number of papers (including Mummery et al. 1991). Therefore, claim 51 is not indefinite. New claim 133 is also added to further define the cell which is derived from VE-like tissue to express alpha-feto protein, as supported by the specification on page 11, lines 1-10, for example. Applicants arguments have been fully considered but are not persuasive.

In the instant case, the phrase "visceral endoderm-like" in claims 51 is vague and renders the claims indefinite because it is unclear as to the metes and bounds of what would be considered "visceral endoderm-like" The phrase "visceral endoderm-like" can mean digestive system cell or tissue, gland cell or tissue, part of respiratory cell or tissue, or no visceral endoderm-like at all. It is unclear what kind of "visceral endoderm-like" or to what extent is intended for the phrase "visceral endoderm-like". It is also unclear what kind of "visceral endoderm-like" cell expresses alpha-feto protein.

Regarding claim **60**, remains rejected for the phrase "substantially" renders the claim indefinite for the reasons of record.

Applicants argue a "substantially confluent" monolayer is clearly understood by the skilled artisan as a layer of cells that almost completely, or completely covers the culture dish

surface. Those skilled in the art who are familiar with cell culture would understand the term "substantially confluent" without ambiguity.

These arguments are not persuasive because the phrase "substantially confluent monolayer" renders the claim indefinite. It is unclear what the term "substantially" is intended to convey, "substantially identical", "substantially different", or "substantially ..."

Therefore, the rejection is maintained.

Claim Rejections - 35 USC § 103/

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45-46, 50-54, 60-61, 64-65, 68-71, 87-89 stand rejected under 35 U.S.C. 103(a) as being unpatentable over **Amit et al** (Developmental Biology, 227: 271-278, 2000) in view of **Mummery et al** (Differentiation, 46: 51-60, 1991); **Rohwedel et al** (Cells Tissues Organs, 165:190-202, 1999 (Abstract)); **Rohwedel et al** (Dev Biol, 164(1): 87-101, 1994 (IDS)) for the reasons of record (office action dated 01/20/2010, pages 3-7).

Applicants argue Amit teaches the use of an embryonic cell type (mouse embryonic fibroblasts) to maintain the hES cells in an undifferentiated state. Applicants in pages 6-12 argue that the Rohwedel 1999, Rohwedel 1994 and Mummery references alone and in combination teach mouse and not human ES cells while Amit teaches human Es cells but

cultured in feeder MEF cells. Applicants argument has been fully considered but is not persuasive.

In the instant case, Rohwedel (1994) teaches that the mouse embryonic carcinoma P19 cells, were induced to differentiate into mesoderm-derived cell types by the FGF-like activity secreted by feeder END-2 cells (p 99, 1st column, 1st paragraph) (emphasis added). Rohwedel (1994) also teaches END-2 cells induce cardiomyogenesis in D3 ES cell-derived aggregates differentiated for 2 days (p 99, 1st column, 1st paragraph) (emphasis added). In addition, Rohwedel (1994) suggests the inducing activity of growth factors depends on the developmental stage of the ES cell line used (p 99, 1st column, 2nd paragraph). Rohwedel (1994) teaches the embryonic carcinoma line PI9 isolated from a teratocarcinoma by ectopic transplantation of a 7.5-day mouse embryo differentiate into mesoderm-derived cell types by the FGF-like activity secreted by feeder END-2 cells, while the ES cell line BLC6 established directly from the inner cell mass show different responses(p 99, 1st column, 2nd paragraph). Rohwedel (1994) also teaches spontaneous myogenin differentiation of human rhabdomyosarcoma cell line (p 101, 1st column (under Shapiro et al incorporation by reference).

Rohwedel (1999) teaches that inhibition of cardiomyocyte differentiation by treatment of embryoid bodies with RA between days 2 and 5 but induction of prominent cardiac differentiation was induced by treatment of embryoid bodies with 10^{-9} M RA after day 5 (p 196, 1st column, 1st and 2nd paragraph). Rohwedel (1999) teaches a nexus between ES cells and EC cells by teaching cellular differentiation by RA has been studied with undifferentiated pluripotent embryonic carcinoma (EC) and ES cells in vitro and both cellular systems are suitable to study differentiation of various cell types, because they recapitulate early stages of mouse embryogenesis (abstract). Rohwedel (1999) teaches modulation of ES cell differentiation in vitro by RA depends on the concentration and developmental stage of application which is

comparable to its stage-dependent influence on embryonic development in vivo (abstract). Similarly, Mummery teaches 10^{-9}M retinoic acid induces differentiation of P19 EC cells into cardiomyocytes cultured in END-2 feeder cells (p 58 figures 5). Mummery suggests RA is involved in the spontaneous differentiation of P19 EC cells in the END-2 system (p 59, 1st column 2nd paragraph). However, even though Mummery and Rohwedel 1994/1999 teach the nexus of END-2 FGF-like activity and RA for the induction of differentiation of mouse ES cells however, one of skill in the art would readily recognize that human ES cell would also be useful to culture with END-2 feeder cells in view of the teachings of Amit that human ES cells cultured on MEFs bFGF maintains the human ES cells in the undifferentiated state thus FGF-like activity secreted by feeder END-2 cells would induce cardiomyocyte differentiation of hES cells, as noted by Rohwedel (1994). One of skill in the art would have used the END-2 feeder cells for human ES cell differentiation particularly in view of the teachings of Amit that identifying the factors that the fibroblasts produce that promote human ES cell renewal will be critical to the large-scale growth of ES cells, because the feeder layers are labor intensive to prepare and because variation between batches of fibroblasts can introduce undesirable variation and complexity to experiments (p277). Amit teaches that serum is a complex mixture that can contain compounds both beneficial and detrimental to human ES cell culture (p 276, 1st column). Different serum batches vary widely in their ability to support vigorous undifferentiated proliferation of human ES cells (p 276). Replacing serum with defined components should reduce the variability of experiments associated with serum batch variation and should allow more carefully defined differentiation studies (p 276). Amit suggests the need for substantial improvements to the serum-free culture of human ES cells (p 276) as well as the fibroblast feeder layer remains the most poorly defined component of the human ES cell culture environment.

Thus the rejection is maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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/Anne-Marie Falk/
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